UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JIANFENG XU, DEBORAH MEYERS, SIGUN ZHENG, PATRICK C. WALSH, WILLIAM B. ISAACS, EUGENE BLEECKER, and DAVID HERRINGTON

Appeal 2009-0938
Application 10/426,262
Technology Center 1600

Decided: March 27, 2009[1]

Before DONALD E. ADAMS, ERIC GRIMES, and RICHARD M. LEBOVITZ, *Administrative Patent Judges.*

LEBOVITZ, *Administrative Patent Judge.*

DECISION ON APPEAL

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[1] The two-month time period for filing an appeal or commencing a civil action, as provided for in 37 C.F.R. § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

This is a decision on appeal from the Examiner's final rejection of claims 1 and 5-8. Jurisdiction for this appeal is under 35 U.S.C. § 6(b). We reverse.

STATEMENT OF THE CASE

"Intense genetic study of familial prostate cancer has resulted in the identification of numerous putative prostate cancer susceptibility loci and several candidate genes, along with a realization of the extensive genetic and etiologic heterogeneity that characterizes this disease" (Spec. ¶8). The Specification describes several mutations in the MSR1 (macrophage scavenger receptor) gene associated with prostate cancer risk (*id.* at ¶¶8, 10).

Claims 1 and 5-8 are pending and stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner contends that the claims contain subject matter not "described in the specification in such a way as to enable one skilled in the art . . . to use the [claimed] invention" (Ans. 4-5). Claim 1 is the only independent claim on appeal. Claims 5-8 depend on claim 1 and incorporate all its limitations. Claim 1 reads as follows:

1. A method of screening a subject for increased risk of prostate cancer, comprising:

detecting the presence or absence of an MSR1 mutation in said subject; and then

determining that said subject is at increased risk of prostate cancer due to the presence or absence of said MSR1 mutation;

said MSR1 mutation selected from the group consisting of the R293X mutation and the DF174Y[2] mutation.

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[2] The original claims refer to the mutation as "DF174Y", but the Specification refers to "D174Y" (Spec. ¶60) as does the Appeal Brief (see p. 3). We use the term "D174Y" throughout this opinion.

ISSUE ON APPEAL

Did the Examiner establish a reasonable basis to question the enablement for the full scope of the claimed method for screening a subject for increased risk of prostate cancer?

PRINCIPLES OF LAW

"[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993)). The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d at 1562.

> It may be difficult to predict, however, whether a novel compound will exhibit pharmacological activity, even when the behavior of analogous compounds is known to those skilled in the art. Consequently, testing is often required to establish practical utility. See, e.g., *Blicke*, 241 F.2d at 720. But the test results need not absolutely prove that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." *Nelson*, 626 F.2d at 856. (emphasis added). In other words, there must be a sufficient correlation between the tests and an asserted pharmacological activity so as to convince those skilled in the art, to a reasonable probability, that the novel compound will exhibit the asserted pharmacological behavior. See *Cross*, 753 F.2d at 1050.

Fujikawa v. Wattanasin, 93 F.3d 1559, 1564 (Fed. Cir. 1996).

FINDINGS OF FACT

Specification

1. The Specification describes mutations in the MSR1 gene, including R293X and D174Y, which indicate an increased risk of prostate cancer in a subject as compared to subjects without the mutation (Spec. ¶¶10, 11, 14).
2. The Specification describes a nonsense mutation, R293X, in Exon 6 of the MSR1 gene (Spec. ¶58). The mutation was observed in four different families, all of whom were Caucasian (*id.*).
3. "The mutation segregates well, although not completely, with prostate cancer in these nuclear families" (Spec. ¶59).
4. The frequency of the R293X mutation was determined in non-hereditary prostate cancer patients ("sporadic") and unaffected men (Spec. ¶65). The mutation "was only found in Caucasian subjects and was more often observed in cases (n=3, 1.3%) than in controls (n=1, 0.6%)" (*id.*).
5. The Specification states that "these results suggest that [the R293X mutation is] low frequency and potentially high penetrance" (Spec. ¶65).
6. The Specification also states that the difference in mutation carrier rates suggests that "the mutation carriers have an increased risk for prostate pathology" (Spec. ¶67).
7. The Specification describes a missense mutation, D174Y, in Exon 4 of the MSR1 gene (Spec. ¶60). The mutation was observed in four African American families (*id.*).
8. The mutation "segregates well, but not completely with prostate cancer in these families" (Spec. ¶60).

9. The D174Y mutation was found more often in prostate cancer cases (n=3, 7%) than in unaffected controls (n=2, 1.8%) (Spec. ¶65).
10. The Specification states that "these results suggest that [the D174Y mutation is] low frequency and potentially high penetrance" (Spec. ¶65).
11. The D174Y mutation appeared more often in African Americans and the R293X mutation more often in Caucasians (Spec. ¶66).

Sun publication[3]

12. Sun describes a meta-analysis of the association of mutations in the MSR1 gene and prostate cancer risk (Sun, at 728). The meta-analysis included a large collection of data from previously published individual studies (*id.* at 729, first column), including those described in the Hope, Seppala, and Lindmark publications (*id.* at 737).
13. "Significant differences were observed for the genotype frequency of R293X . . . between sporadic prostate cancer patients and controls" (Sun, at 730, first column).
14. "When the meta-analysis for R293X was performed by excluding the initial report, [Sun] did not observe evidence of a significant association" (Sun, at 730, second column).
15. "A significantly increased risk was observed in D174Y carriers when a fixed effect was assumed" (Sun, at 730, second column).
16. When the initial report was excluded, Sun "did not observe evidence of a significant association" (Sun, at 730, second column).

[3] Sun et al., "Meta-analysis of Association of Rare Mutations and Common Sequence Variants in the *MSR1* Gene and Prostate Cancer Risk", *The Prostate*, 66:728-737 (2006).

17.

> Overall, there was evidence for association between sporadic prostate cancer risk and R293X among white men, and evidence for . . . D174Y . . . among black men. However, other pieces of evidence do not corroborate our overall findings: results from meta analysis of [R293X and D174Y] were not statistically significant when the initial report was excluded . . . ; there is a lack of evidence supporting an association between R293X and hereditary/familial prostate cancer.

(Sun, at 735, second column.)

18. After discussing several of the published studies on the R293X mutation, including several reporting no association with prostate cancer, Sun concludes:

> Taken together, our results suggest that R293X is unlikely to be a highly penetrant variant that leads to familial and hereditary prostate cancer; however, it may confer a moderate risk to sporadic prostate cancer.

(Sun, at 736, second column.)

19. For the D174Y mutation, Sun states that "there is reasonable evidence to suggest that the D174Y mutation may confer a moderate risk to prostate cancer among black men" (Sun, at 736, second column).

ANALYSIS

The dispute in this appeal involves the question of whether the Specification teaches how to use the claimed method of screening a subject for increased risk of prostate cancer comprising detecting the presence of the R293X and D174Y mutations in the MSR1 gene.

After reviewing the evidence in the Specification describing the relationship between the R293X and D174Y mutations and prostate cancer,

the Examiner concludes that it "has not [been] shown that the correlation between the claimed mutations and the risk of both sporadic and hereditary prostate cancers is significant in all populations" (Ans. 11). The Examiner contends that post-filing date published references – Hope, Seppala, and Lindmark – show "that there is no statistically significant association between mutations in MSR1 and the risk of prostate cancer" (*id.* at 9).

The Examiner also cites pre-filing date publications which provide evidence of the unpredictability in the relationship between gene mutations and disease (*id.* at 6-8). None of these pre-filing date publications describe the MSR1 gene or MSR1 gene mutations, but rather generically discuss the field.

Based on the evidence, the Examiner concludes:

> In order for one skilled in the art to use the claimed method to screen a subject for increase risk of prostate cancer, the claimed MSR1 mutations must correlate to the risk of prostate cancer, and such correlation must be statistically significant. Without such correlation, one skilled in the art would not be able to screen a subject for the risk of the prostate cancer.

(Ans. 12.)

We have carefully considered the evidence proffered by the Examiner, but are not persuaded that the Examiner met the burden of establishing a reasonable basis to question the enablement provided for the claimed invention.

The Specification provides evidence that the R293X and D174Y mutations occurred in several families with familial or hereditary prostate cancer (Finding of Fact ("FF") 2, 3, 7, & 8). The mutation was not always associated with prostate cancer (FF3, 8). However, 100% correspondence is not necessary to meet the limitation of claim 1 of an "increased risk of

prostate cancer." As we interpret the claim, an "increased risk" would be understood to mean an increased possibility or probability of getting prostate cancer when the mutation is present. That limitation is met by the disclosure that the R293X and D174Y mutations segregate "well", but not "completely" with prostate cancer in the identified families (FF3, 8) because it indicates an increased probability of getting cancer.

In addition to the occurrence of the mutations in hereditary prostate cancers, the Specification also describes their occurrence in sporadic cases. The Specification reports that the R293X and D174Y mutations occur at a low frequency in the population but that each is associated with an increased risk of prostate cancer (FF4-6, 9, & 10).

The Examiner does not appear to question the data in the Specification, but contends that the enablement problem stems from the fact that the elevated risk is not present in all populations (Ans. 11). The Examiner's complaint is apparently based on the Specification disclosure that the hereditary R293X mutation was found in Caucasians, the hereditary D174Y mutation in African Americans, and the same racial pattern for the sporadic R293X and D174Y mutations (FF11).

"[I]t is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. *See In re Angstadt*, 537 F.2d 498, 504 (CCPA 1976)." *Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005). Thus, while it may be true that the Specification's teachings indicate that the elevated cancer risk for the R293X and D174Y mutations might be correlated with a subject's race, there is still sufficient evidence that the generic claim for

detecting increased prostate cancer risk is enabled by the Specification. It is not a function of the claims to specifically exclude possible inoperative embodiments. *Atlas Powder Company v. E.I. Du Pont De Nemours & Company*, 750 F.2d 1569, 1577 (Fed. Cir. 1984).

The Examiner also contends that the Specification does not enable the claimed method because there is not a "significant correlation" between prostate cancer risk and the R293X and D174Y mutations (Ans. 12). The Examiner's conclusion is based on post-filing publications which determined the incidence of R293X and D174Y mutations, and concluded they were not associated with a cancer risk (*id.* at 9).

It is unnecessary for Appellants to prove with 100% certainty that a correlation exists between the R293X and D174Y mutations and an increased prostate cancer risk. It is sufficient that that the evidence is "reasonably indicative" that a correlation is present. As the Federal Circuit put it in *Fujikawa v. Wattanasin*, 93 F.3d at 1564, "there must be a sufficient correlation between the tests and an asserted pharmacological activity so as to convince those skilled in the art, to a reasonable probability, that the novel compound will exhibit the asserted pharmacological behavior."

There is no reason to treat a gene mutation, whose activity is to elevate prostate cancer risk, differently from a compound having a useful pharmacological activity. Each possesses a desired biological and medically relevant activity. Thus, the question boils down to whether a person of skill in the art would have been convinced that the R293X and D174Y mutations increase the risk of prostate cancer as required by claim 1. *Fujikawa v. Wattanasin*, 93 F.3d at 1564.

The Sun publication analyzed several independent published studies involving the association of MSR1 and prostate cancer, including the Seppala, Hope, and Lindmark papers cited in the Examiner's Answer (FF12). Despite acknowledging that not all the studies supported an elevated prostate cancer risk with the R293X and D174Y mutations (FF14, 16, 17), Sun went on to conclude that R293X "may confer a moderate risk to sporadic prostate cancer" (FF18) and that "there is reasonable evidence to suggest that the D174Y mutation may confer a moderate risk to prostate cancer among black men" (FF19). As it is unchallenged that the Sun publication was authored by persons of ordinary skill in the pertinent field of invention, we consider these statements as evidence that such persons were convinced "to a reasonable probability" that the R293X and D174Y gene mutations are associated with an increased risk of prostate cancer as recited in claim 1.

The Examiner admits that Sun teaches "at best that there is a correlation of R293X and risk of sporadic prostate cancer in white man, and a correlation of D174Y and risk of sporadic prostate cancer in black man" (Ans. 13-14). The Examiner nonetheless rejects this evidence because the elevated risk is not in all populations. As explained above, it is unnecessary for the claims to exclude all inoperative embodiments as long as the generic invention is enabled. Here, there is ample evidence that the Specification teaches how to use the recited mutations to determine prostate cancer risk (FF2-10).

CONCLUSION OF LAW

The Examiner did not establish a reasonable basis to question the enablement for the full scope of the claimed method for screening a subject for increased risk of prostate cancer. We reverse the rejection of claims 1 and 5-8.

REVERSED

Ssc:

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